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TOTAL SYNTHESIS OF (±)-METHYL 3-(3-ISOCYANO-6-OXABICYCLO[3.1.0]HEX-2-EN-5-YL)-2-PROPENOATE

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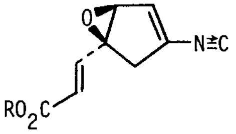
Summary: The total synthesis of (±)-methyl 3-(3-isocyano-6-oxabicyclo[3.1.0]hex-2-en-5-yl)-2-propenoate has been achieved using 3-tosyl-2-azabicyclo[2.2.1]hepta-2,5-diene as a key starting material.

The isonitrile acid 1 has been isolated from cultures of the fungus *Trichoderma hamatum* (Bon.) Bain. aggr. and might be responsible for poor ruminant growth in permanent pasture.[1] The structure of the unstable acid was established as the relatively stable crystalline methyl ester 2 by X-ray diffraction analysis. The acid is composed of a unique γ,δ-epoxy-α,β-unsaturated isonitrile. Herein we report the first total synthesis of the racemic methyl ester 2.

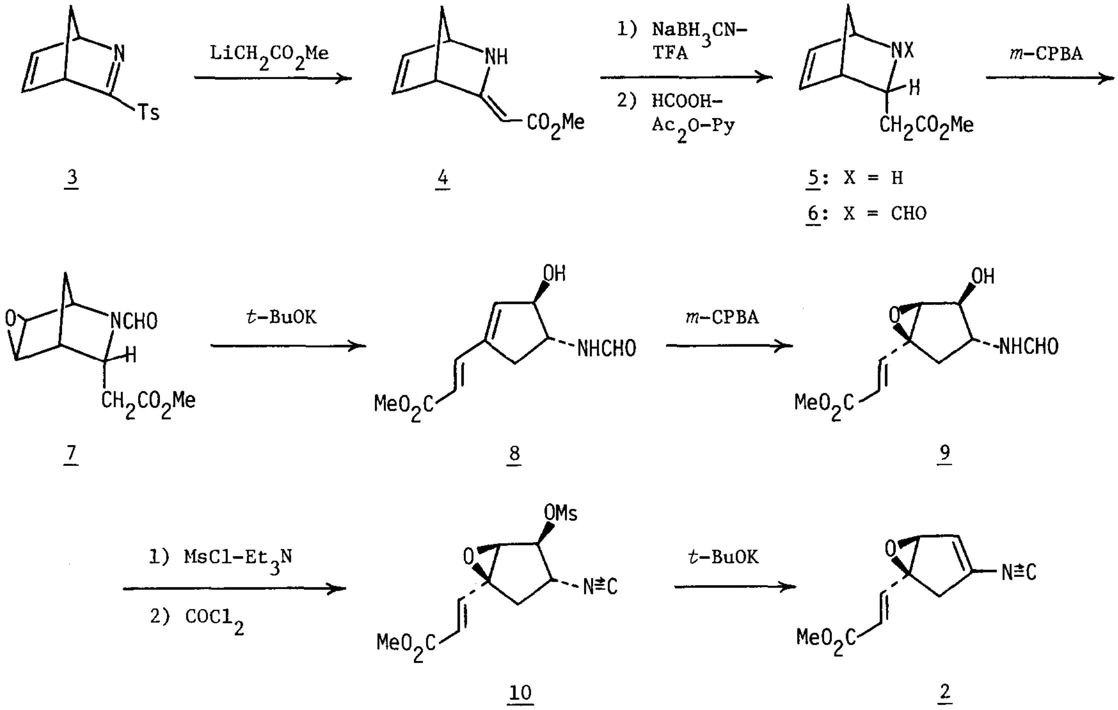


1: R = H

2: R = Me

Treatment of 3-tosyl-2-azabicyclo[2.2.1]hepta-2,5-diene[2] 3 with 2 equivalents of methyl acetate carbanion in THF (-78° → r.t.) afforded the β-amino-α,β-unsaturated ester 4[3] in 81% yield. Reduction of 4 with $NaBH_3CN$ and CF_3COOH in methanol at room temperature gave exclusively the *endo*-product 5, which was converted to the formamide 6 (Ac_2O, HCOOH, Py, r.t.) in 80% overall yield from 4. Epoxidation of 6 with *m*-CPBA took place from the less hindered side, giving solely the *exo*-epoxide 7 (67%). When 7 was treated with 0.5 equivalent of *t*-BuOK/*t*-BuOH in THF at room temperature, double cleavage of the bicyclic system and the epoxide occurred to give the desired diene ester 8[4] in 53% yield.

Regio- and stereospecific epoxidation of 8 was realized by using *m*-CPBA to give the hydroxy epoxide 9[5] (68%). The epoxide was introduced from the same side as the hydroxy group.[6] One-pot conversion of the hydroxy formamide 9 into the isocyanide 10[7] was effected by treatment of 9 with MsCl and Et_3N (excess) in CH_2Cl_2 followed by addition of phosgene[8] (89%). Elimination of the mesylate 10 using 5 equivalents of *t*-BuOK in THF-toluene (1:6) at -78° yielded the unstable α,β-unsaturated isonitrile 2 (oil, 53%). The synthetic isonitrile ester 2 was identical in TLC behavior and spectral (^1H NMR, ^{13}C NMR, and MS) properties with the natural product.[9]



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References and Notes

1. D. Brewer, E. J. Gabe, A. W. Hanson, A. Taylor, J. W. Keeping, V. Thaller, and B. C. Das, J. Chem. Soc., Chem. Commun., 1061 (1979).
2. J. C. Jagt and A. M. van Leusen, J. Org. Chem., 39, 564 (1974).
3. mp 79-81°; ^{1}H NMR ($CDCl_3$) δ 1.7-2.1 (2H, m) 3.53 (1H, m), 3.64 (3H, s), 4.51 (1H, m), 5.02 (1H, s), 6.51 (2H, m), 6.82 (1H, br s).
4. mp 116-118°; ^{1}H NMR ($CDCl_3$) δ 2.32 (1H, dd, J = 8, 15.5 Hz), 3.04 (1H, dd, J = 8.5, 15.5 Hz), 3.78 (3H, s), 4.20 (1H, m), 4.80 (1H, br s), 5.82 (1H, d, J = 15 Hz), 6.12 (1H, s), 6.43 (1H, br s), 7.40 (1H, d, J = 15 Hz), 8.20 (1H, s).
5. mp 140-141°; ^{1}H NMR ($CDCl_3$) δ 1.98 (1H, dd, J = 9, 13 Hz), 2.52 (1H, dd, J = 8, 13 Hz), 3.59 (1H, d, J = 1 Hz), 3.77 (3H, s), 3.90 (1H, m), 4.15 (1H, dd, J = 1, 7 Hz), 6.10 (1H, d, J = 15.5 Hz), 6.80 (1H, d, J = 15.5 Hz), 8.07 (1H, s).
6. H. B. Henbest, Proc. Chem. Soc., 159 (1963).
7. mp 123-125°; ^{1}H NMR ($CDCl_3$) δ 2.32 (1H, dd, J = 9, 13 Hz), 2.82 (1H, dd, J = 8, 13 Hz), 3.20 (3H, s), 3.77 (3H, s), 3.82 (1H, m), 3.85 (1H, d, J = 1 Hz), 5.16 (1H, dd, J = 1, 7.5 Hz), 6.12 (1H, d, J = 15.5 Hz), 6.74 (1H, d, J = 15.5 Hz); IR (CH_2Cl_2) 2150, 1725, 1370, 1175 cm^{-1}.
8. I. Ugi, U. Fetzer, U. Eholzer, H. Knupfer, and K. Offermann, Angew. Chem. Intern. Ed., 4, 472 (1965).
9. We are indebted to Professor R. J. Parry, Rice University, for a sample of the natural isonitrile ester.

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